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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/319,724	09/08/1999	GERLINDE LENZEN	045636-5025	3497

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/319,724	LENZEN ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,23,25,26,29-46 and 49* is/are pending in the application.

4a) Of the above claim(s) *30-32,38 and 40-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *22,25,29,33,34,36,37,39 and 49* is/are rejected.

7)☐ Claim(s) *23,26 and 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 6/7/05, have been entered in full.

Claims 30-32, 38, 40-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, as set forth previously.

Applicant is notified that any outstanding rejection or objection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments and/or Applicant's persuasive arguments.

Response to Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 25, 29, 33, 34, 36, 37, 39, 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding a protein of SEQ ID NO: 14 and the portion thereof capable of binding ICYP i.e. SEQ ID NO: 1,

does not reasonably provide enablement for polynucleotides that do not encode a polypeptide of SEQ ID NO: 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention as currently claimed, as set forth below.

The specification asserts that the polypeptides of SEQ ID NO: 1 and 14 are capable of inhibiting eosinophil chemotaxis and mediation of depolarized-intestinal smooth muscle relaxation and are useful in the study of ICYP transduction and drug development, yet the claims claim a vast genus of polypeptide variants of either SEQ ID NO: 1 or 14, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 1 or 14. Applicant has not provided sufficient guidance as to how to make and use the polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 1 or 14, but which still retain a useful property of the polypeptide of SEQ ID NO: 1 or 14. The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 1 or 14 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 1 or 14 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 1 or 14, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 1 or 14

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any

given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 14 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely

an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the incalculable number of variants recited in the claims and screen same for activity, such a screen not being known in the art or taught in the specification, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Applicant argues that the claims have been amended to require the measurement of relaxation of depolarized-intestinal smooth muscle, and as such are fully enabled. This argument has been fully considered but not deemed persuasive for the same reason as that regarding inhibiting eosinophil chemotaxis, as set forth previously, there does not appear to be a method known in the art for screening for functional variants that mediate inhibition of eosinophil chemotaxis nor for a method for screening for functional variants that mediate relaxation of depolarized-intestinal smooth muscle. That it is possible to measure inhibition of eosinophil chemotaxis and relaxation of depolarized-intestinal smooth muscle is not in dispute, rather, no

teaching of an assay that screens for functional variants of the instant polypeptides is provided nor known in the art. Simply verbalizing that this can be done, does not teach one how to do it, particularly without undue experimentation.

Claims 22, 25, 29, 33, 34, 36, 37, 39, 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth previously and reiterated below:

The specification discloses a polynucleotide of SEQ ID NO: 13 and a portion thereof SEQ ID NO: 2, yet the claims encompass polynucleotides not described in the specification, i.e. sequences from other species, mutated sequences, allelic variants, or artificial sequences that hybridize to SEQ ID NO: 13. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 13, and a single portion thereof SEQ ID NO: 2, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs,

defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence SEQ ID NO: 13, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlations, methods of making the claimed product, or combination thereof. In this case, the only factor present in the claim is a requirement that the variants be sufficiently structurally related so that they hybridize to the reference sequences under specified conditions. With the exception of the small peptides of SEQ ID NO: 5 and 6 as recited in claim 49, there is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Thus, with the exception of the polynucleotide of SEQ ID NO: 2 and 13, and other polynucleotides which encode a polypeptide of SEQ ID NO: 1 or 14, the skilled artisan cannot envision encompassed variants. Therefore, only polynucleotides encoding a polypeptide of SEQ ID NO: 1 or 14, and polynucleotides *consisting* of fragments thereof, or polynucleotides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but

not the full breadth of the claims meet the written description provision of 35 U.S.C. ∋112, first paragraph.

Applicant argues that the specification in Example 1 describes the rat protein. This argument has been fully considered but not deemed persuasive. The examiner can find only a 17 amino acid peptide from the rat. No other information is given for the full length protein and there is no asserted correlation between the structure of this peptide and any function. This is also true of SEQ ID NO: 5 and 6.

Applicant argues that the claims are in conformance with Example 9 of the written description training materials. This argument has been fully considered but not deemed persuasive. In Example 9 the specification discloses the clones were assayed for adenylate cyclase activity. The instant specification discloses no such assay for isolated clones that mediate depolarized-intestinal smooth muscle, and nor is such known in the art.

Allowable Subject Matter

Claims 23, 26, and 35 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Conclusion

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

This application contains claims 30-32, 38, 40-46 drawn to an invention nonelected with traverse in Applicant's response of 9/3/02. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX months.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

August 18, 2005

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER